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Review Article

Fesoterodine, an advanced antimuscarinic for the treatment of overactive bladder: A safety update

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Abstract

The pillars of pharmacotherapy for overactive bladder (OAB) are antimuscarinic agents which inhibit bladder smooth muscle contractions through interference with acetylcholine action on muscarinic receptors of the detrusor smooth muscle. Despite the availability of different antimuscarinic compounds, physicians and patients remain dissatisfied with current treatments due to adverse events and/or insufficient efficacy. Therefore, new agents with improved safety and efficacy profiles are needed for a more effective treatment of overactive bladder.

Fesoterodine is a novel bladder-selective muscarinic antagonist that has shown potent antimuscarinic activity *in vitro* and *in vivo.* In multiple investigations, the agent has been shown to be safe and well tolerated in subjects of different ethnic origin, age and gender; in poor and extensive CYP2D6 metabolizers; in subjects taking concomitant medication inhibiting CYP3A4; in fed or fasted states; and in those suffering from hepatic impairment. No clinically relevant changes in heart rate, blood pressure, ECG parameters or laboratory analyses have been seen with therapeutic doses of fesoterodine in these studies.

Furthermore, in a phase II clinical trial in patients with OAB, fesoterodine demonstrated rapid and significant efficacy on a variety of endpoints. The results of this trial encouraged the manufacturer (SCHWARZ PHARMA) to initiate a phase III clinical trial program for fesoterodine.

Introduction

Overactive bladder (OAB) is an extremely common disorder, affecting up to 33 million adults in the United States and 17% of the adult population in major European countries (1, 2). OAB can occur at any age and in either gender, although its prevalence is higher in geriatric and female populations.

OAB is a bladder function disorder resulting in symptoms of urgency, with or without urge incontinence, and usually includes increased urinary frequency and nocturia (3). The disorder is due to spastic contractions of the detrusor muscle of the bladder, resulting in sustained high bladder pressure and the urgent need to urinate. This can be caused by several reasons, such as traumatic or toxic nerve damage (*e.g.*, abdominal trauma, pelvic trauma or surgery, bladder stones, adverse effects of drugs), neurological diseases (*e.g.*, spinal cord lesions, multiple sclerosis, Parkinson's disease, excessive neurotransmitter release in the bladder) or myogenic instability (*e.g.*, bladder hypertrophy caused by outlet obstruction or urinary tract infection) (4).

In some cases, OAB can be managed without pharmacotherapy, using exercise, pessaries, implants, biofeedback or behavioral therapy. But in most cases, pharmacotherapy is the better option. Anticholinergic agents have been found to be particularly effective for treating OAB. During normal micturition, acetylcholine released from postganglionic parasympathetic neurons acts on the muscarinic receptors of the detrusor smooth muscle in the bladder to stimulate contractions. Anticholinergic agents interfere with this action, thus reducing detrusor contractions. However, despite the availability of different antimuscarinic drugs, physicians and patients remain dissatisfied with current treatments due to adverse events and/or insufficient efficacy (4-8). Therefore, new agents with improved safety and efficacy are needed for a more effective treatment of OAB.

Fesoterodine is a novel bladder-selective antimuscarinic for the treatment of OAB. The agent is orally administered once daily and is rapidly and extensively hydrolyzed to its active metabolite, SPM 7605. Based on excellent results in several phase I and phase II trials, fesoterodine is expected to show an improved efficacy-safety ratio compared to current antimuscarinics.

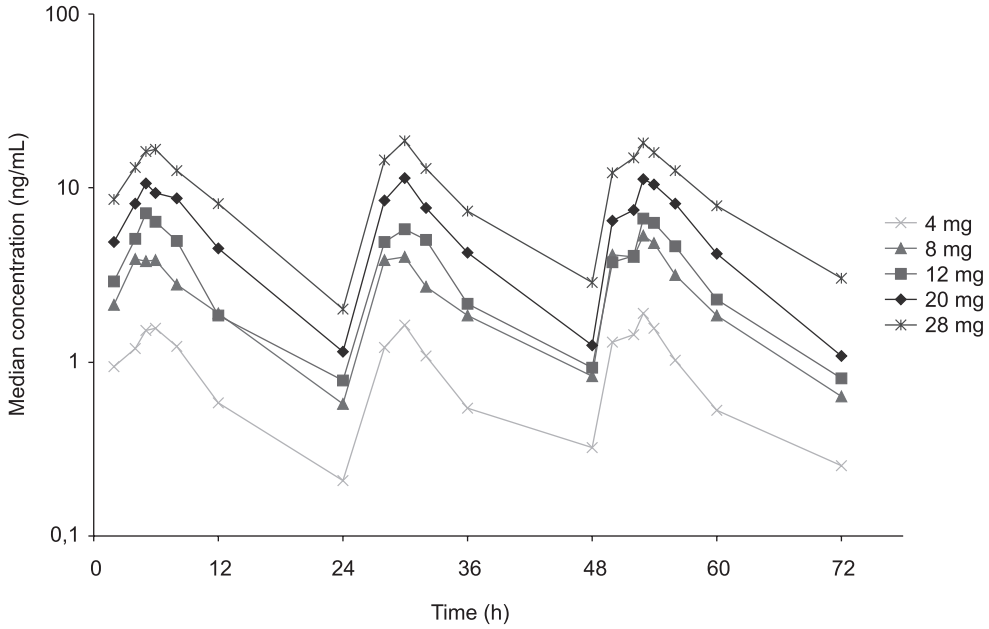

Fig.1. SPM 7605 plasma concentrations after administration of multiple oral ascending doses of fesoterodine (14-16).

Pharmacological Actions

The pharmacodynamic effects of fesoterodine and its active metabolite, SPM 7605, were examined *in vitro* on carbachol- and electrical field stimulation-induced contractions of rat bladder strips and after i.v. administration (0.01, 0.1 and 1 mg/kg) to healthy rats *in vivo*. Fesoterodine and SPM 7605 (1 μM-1 mM) shifted the concentration-response curve for carbachol to the right, with no significant depression of the maximum, suggesting competitive antagonism. The pA_2 values were 8.7 ± 0.3 and 8.8 ± 0.3, respectively, and the slopes of the Schild plot were 1 and 1.3, respectively. Similar pA_2 values were obtained for oxybutynin and atropine: 8.4 ± 0.1 and 9.0 ± 0.3, respectively. Both fesoterodine and SPM 7605 inhibited electrical field stimulation-induced contractions in a concentration-dependent manner, with maximum inhibition (60.0 ± 15.3 and 46.6 ± 13.1%, respectively) observed at a concentration of 0.1 μM. In contrast, the maximum inhibition observed with 0.1 μM of oxybutynin and atropine was 33.7 ± 14.0 and 39.7 ± 27.1%, respectively (12). In conclusion, the *in vitro* functional data indicate that fesoterodine and SPM 7605 are more potent than oxybutynin and atropine.

Administration of fesoterodine and SPM 7605 (0.01 mg/kg i.v.) to healthy rats resulted in significant increases in bladder capacity and intercontraction intervals 90-120 min postdosing; micturition volume only slightly increased at this dose. Significant reductions in micturition pressure were observed for both agents at this dose, indicating that the threshold dose was less than 0.01 mg/kg (12).

Pharmacokinetics

After oral administration, fesoterodine cannot be detected in plasma due to rapid and extensive hydrolyzation by unspecific plasma esterases to its active metabolite SPM 7605. After single- or multiple-dose administration of fesoterodine at doses of 4-28 mg, SPM 7605 shows dose-proportional pharmacokinetics. Maximum plasma levels are reached after approximately 5 hours (Fig. 1). No accumulation occurs after multiple-dose administration (13-16).

The terminal half-life of SPM 7605 is approximately 7 hours. SPM 7605 is eliminated via direct renal secretion and via hepatic biotransformation into considerably less active metabolites. The hepatic metabolization involves different cytochrome P450 (CYP) enzymes such as CYP3A4 and CYP2D6. Approximately 7% of the Caucasian population are poor metabolizers for CYP2D6 and are essentially devoid of this enzyme activity. SPM 7605 plasma levels are almost 2-fold increased in poor CYP2D6 metabolizers. Due to the fact that the terminal half-life of SPM 7605 is not changed in poor CYP2D6 metabolizers, this difference is not considered clinically relevant (Fig. 2) (13).

Special populations

Comparison of the pharmacokinetics in elderly males and females (>65 years) with the pharmacokinetics in young subjects (18-45 years) shows similar body weight

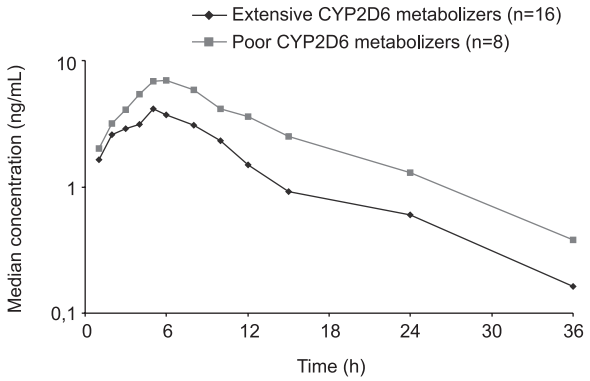

Fig. 2. SPM 7605 plasma concentrations after administration of a single oral dose of 8 mg fesoterodine to extensive and poor metabolizers for CYP2D6 (13).

normalized maximum plasma levels and area under the curve values for SPM 7605 in all three populations (Fig. 3). No differences in pharmacokinetic parameters are observed (17). A comparsion between Caucasian and Black African subjects shows similar SPM 7605 plasma concentrations and pharmacokinetic parameters in both groups (Fig. 4) (18).

Dose adjustments also do not appear to be necessary in patients with mild to moderate hepatic impairment, as indicated by the results of a trial in 8 patients with moderate hepatic impairment and 8 age- and weight-matched healthy subjects. In the open-label trial, single 8 mg doses of fesoterodine were investigated. Both study groups were comprised of male Caucasians. Compared to the healthy subjects, those with liver impairment had increased SPM 7605 exposure, with C_{max} values increased 1.4-fold and AUC values increased 2.2-fold (Fig. 5). While the mean t_{max} was lengthened from 5.4 hours in healthy subjects to 7.4 hours in patients with hepatic impairment, the mean $t_{1/2}$ value was similar between groups (8.4 ± 1.5 and 8.9 ± 2.1 hours, respectively). The unchanged terminal half-life in patients with liver impairment suggests no accumulation of SPM 7605. Therefore, no adjustments in the dose of fesoterodine

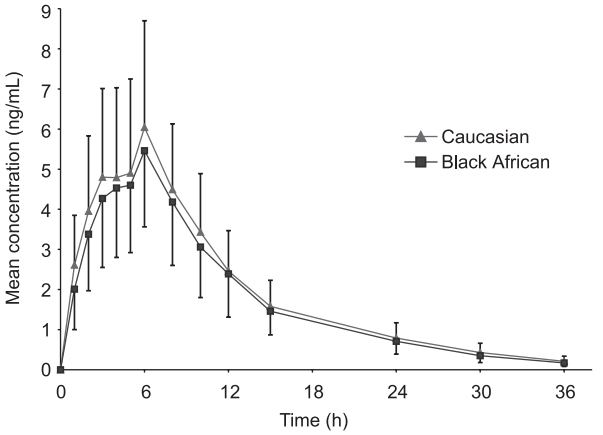

Fig. 4. Arithmetic mean (± SD) of SPM 7605 plasma concentrations after administration of a single oral dose of 8 mg fesoterodine to healthy male Caucasian and Black African subjects (n=12 per group) (18).

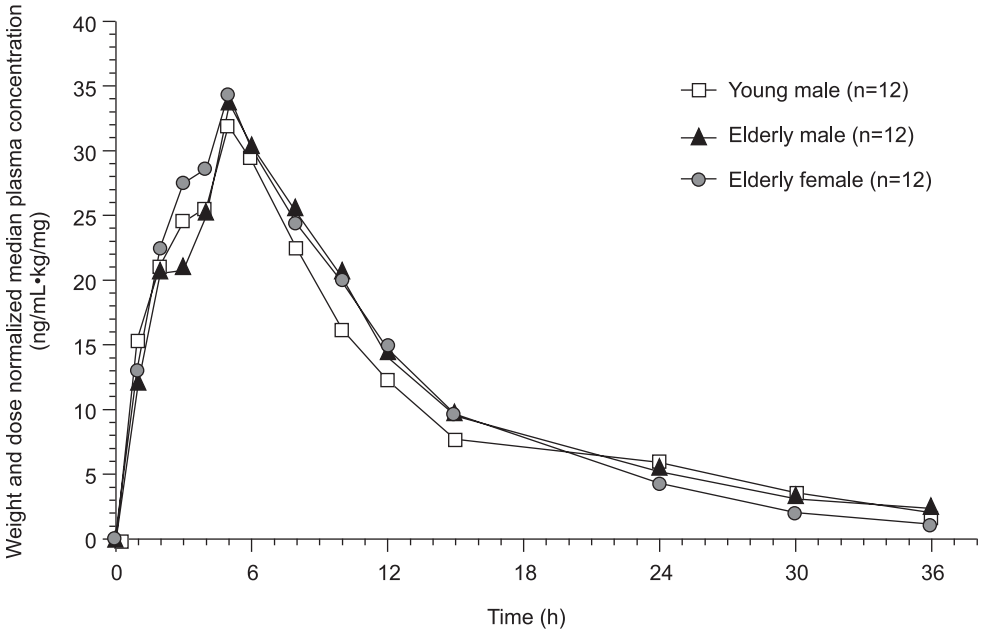

Fig. 3. SPM 7605 body weight and dose normalized plasma concentrations after administration of a single oral dose of 8 mg fesoterodine in young male, elderly male and elderly female subjects (n=12 per group; median) (17).

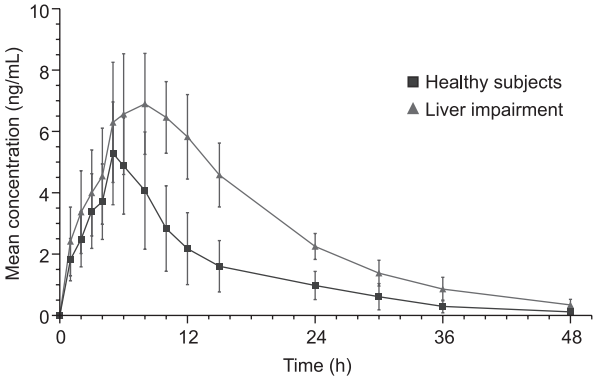

Fig. 5. Plasma concentrations of SPM 7605 and its metabolites after administration of a single oral dose of 8 mg fesoterodine (arithmetic means ± SD; n=8 healthy subjects, n=8 patients with moderate liver impairment).

appear to be warranted when administered to patients with mild or moderate liver impairment (20).

Concomitant treatments

The effects of concomitant treatment with the potent CYP3A4 inhibitor ketoconazole on the safety and pharmacokinetics of fesoterodine were investigated in extensive and poor metabolizers for CYP2D6. In this trial, fesoterodine was safe and well tolerated alone or together with ketoconazole both in poor and extensive CYP2D6 metabolizers. Concomitant ketoconazole treatment resulted in an increase in SPM 7605 plasma concentrations caused by CYP3A4 inhibition. However, as shown by a slight 1.5-fold increase in C_{max} in poor CYP2D6 metabolizers (Fig. 6) and by the unchanged terminal half-life, other elimination pathways are able to compensate for a blockade of two important hepatic metabolism steps. Despite the statistical significance of this pharmacokinetic interaction, the increase in plasma levels is small and was not considered to be clinically relevant (19).

Food effect

The effect of food on the pharmacokinetics of fesoterodine was evaluated in an open-label, crossover study in which 16 healthy male subjects received an 8 mg dose of fesoterodine in the fasted state and after eating a high-fat, high-calorie meal. Time to reach C_{max} was not influenced by the ingestion of food. The pharmacokinetic parameters C_{max} and $AUC_{0\text{-}tz}$ increased slightly in the fed condition. Bioavailability of SPM 7605 expressed as $AUC_{0\text{-}inf}$ was on average 12% higher for fesoterodine administered in the fed state than in the fasted state. The differences in the pharmacokinetics of SPM 7605 seen in fed subjects did not appear to be great enough to warrant consideration of meals when administering fesoterodine (21).

Electrocardiogram

Electrocardiogram data from 6 phase I trials have been retrospectively analyzed, including ECGs taken prior to treatment, at maximum concentrations and at follow-up. The analysis concluded that fesoterodine had no direct effect on myocardial repolarization when given in single and multiple doses up to 28 mg/day (23).

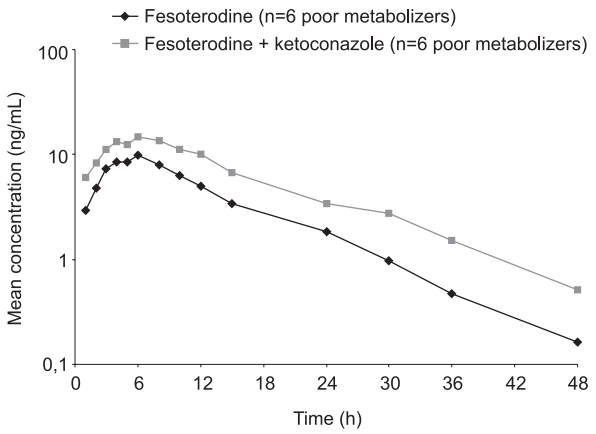

Fig. 6. SPM 7605 plasma concentrations after administration of a single dose of 8 mg fesoterodine alone or together with a pre- and cotreatment with ketoconazole in poor CYP2D6 metabolizers (19).

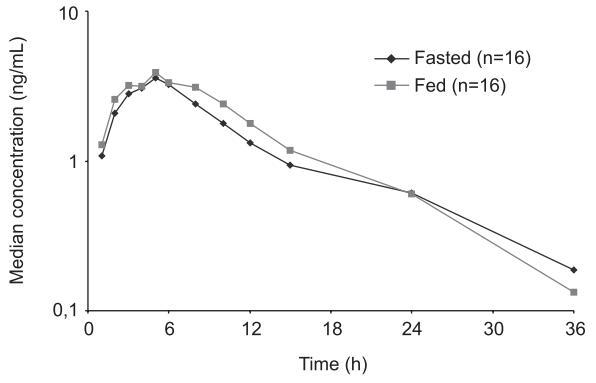

Fig. 7. Influence of concomitant food intake on SPM 7605 plasma concentrations (fed: n=16, fasted: n=16) (21).

Phase II clinical evaluation

At doses of 4, 8 and 12 mg o.d., fesoterodine demonstrated efficacy and safety in a phase II trial in 728 patients with OAB. The best balance of activity and tolerability was seen with the 4- and 8-mg doses. At sites in

Table I: Adverse events with a frequency greater than 1% in any treatment group and dropouts due to adverse events (22).

	Placebo (n=183)	Fesoterodine 4 mg (n=186)	Fesoterodine 8 mg (n=173)	Fesoterodine 12 mg (n=186)
Dry mouth*	9%	25%	26%	34%
Headache	16%	17%	16%	15%
Nausea	7%	5%	2%	6%
Constipation	3%	2%	3%	6%
Dizziness	3%	4%	1%	2%
Abnormal vision	1%	0%	0%	1%
Drop outs	4%	6%	2%	12%

*After randomization

Europe, Israel and South Africa, patients were randomized to 12 weeks of active treatment or placebo.

Safety results of this phase II clinical trial showed that the occurrence of adverse events, including constipation and vision disorders, was similar between the placebo and active treatment groups. No safety issues arose, and vital signs and ECG parameters were not significantly affected by treatment. Dropout rates due to adverse events were 4% of subjects in the placebo group, and 6%, 2% and 12% in the 4 mg, 8 mg and 12 mg fesoterodine groups, respectively (22).

The most common adverse event was dry mouth, which was reported in 9%, 25%, 26% and 34% of patients in the placebo and fesoterodine 4-, 8- and 12-mg groups, respectively (Table I). Dry mouth was mostly mild to moderate in severity (22).

Fesoterodine is now in phase III clinical development, and approximately 2,000 patients with overactive bladder syndrome are expected to be enrolled in 12-week trials in Europe and the United States (24).

References

1. Highlights from the World Health Organization. 2nd International Consultation on Incontinence. July 1-4, 2001, Paris, France. *Increasing awareness and improving the care of urinary incontinence*. Rev Urol 2003, 5(1): 22-5.

2. Milsom, I., Abrams, P., Cardozo, L., Roberts, R.G., Thüroff, J., Wein, A.J. *How wide spread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study*. BJU International 2001, 87: 760-6.

3. Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten U. et al. *The standardization of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society*. Urology 2003, 61: 37-49.

4. Prous Science Drug R&D *Backgrounders: Urinary incontinence (online publication)*. Updated May 15, 2003.

5. Sullivan, J., Abrams, P. *Pharmacological management of incontinence*. Eur Urol 1999, 36(Suppl. 1): 89.

6. Andersson, K.E., Appell, R., Cardozo, L.D., Chapple, C., Drutz, H.P., Finkbeiner, A.E., Haab, F., Vela Navarrete, R. *The pharmacological treatment of urinary incontinence*. BJU Int 1999, 84: 923-47.

7. Eglen, R.M., Choppin, A., Dillon, M.P., Hegde, S. *Muscarinic receptor ligands and their therapeutic potential*. Curr Opin Chem Biol 1999, 3: 426-32.

8. Andersson, K.E. *Drug therapy for urinary incontinence*. Baillière's Best Pract Res Clin Obstet Gynaecol 2000, 14: 291-313.

9. Chapple, C., Jonas, U., Chancellor, M., Ridder, A. *New antimuscarinic agent, solifenacin succinate, reduces urgency episodes in overactive bladder: An analysis of over 3000 patients*. XIXth Cong Eur Assoc Urol, March 24-27 2004, Vienna: Abst. 508.

10. Chapple, C. *Darifenacin is effective in improving the major symptoms of overactive bladder: A pooled analysis of phase III studies*. XIXth Cong Eur Assoc Urol, March 24-27 2004, Vienna: Abst. 512.

11. Wesnes, K., Lipton, R., Kolodner, K., Edgar, C. *Darifenacin, an M_3 selective receptor antagonist for the treatment of overactive bladder, does not affect cognitive function in elderly volunteers*. XIXth Cong Eur Assoc Urol, March 24-27 2004, Vienna: Abst. 513.

12. Breidenbach, A., Pandita, R., Selve, N., Andersson, K. *Pharmacodynamic profiling of the novel antimuscarinic drug fesoterodine on rat bladder*. 32nd Annu Meet Int Continence Soc (Aug 28-30, Heidelberg) 2002, Abst 448.

13. Sachse, R., Cawello, W., Haag, C., Horstmann, R. *Dose-proportional pharmacokinetics of the new antimuscarinic fesoterodine*. Naunyn-Schmied Arch Pharmacol 2003, 367(Suppl. 1): Abst 446.

14. Sachse, R., Cawello, W., Haag, C., Horstmann, R. *Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel bladder-selective antimuscarinic fesoterodine*. Eur Urol Suppl 2003, 2(1): Abst 111.

15. Sachse, R., Cawello, W., Auer, S., Horstmann, R. *Pharmacodynamics of multiple dose treatment with the novel antimuscarinic drug fesoterodine*. Naunyn-Schmied Arch Pharmacol 2002, 365(Suppl. 1): Abst 413.

16. Cawello, W., Auer, S., Hammes, W., Sachse, R., Horstmann, R. *Multiple dose pharmacokinetics of fesoterodine in human subjects*. Naunyn-Schmied Arch Pharmacol 2002, 365(Suppl. 1): Abst 428.

17. Sachse, R., Cawello, W., Hammes, W., Horstmann, R. *Safety and pharmacokinetics of the novel antimuscarinic drug fesoterodine in populations of different age or gender*. 32nd Annu Meet Int Continence Soc (Aug 28-30, Heidelberg) 2002, Abst 440.

18. Sachse, R., W. Cawello, Hammes, W., Horstmann, R. *Safety and pharmacokinetics of the novel bladder-selective antimuscarinic fesoterodine in populations of different ethnic origin*. Proceedings of the International Continence Society 2003, 33: 377

19. *Safety, tolerability and pharmacokinetics of fesoterodine after co-treatment with the potent cytochrome P450 3A4 inhibitor ketoconazole.* ICS/IUGA Ann Meet. Paris, France, Aug. 25-27 2004.

20. *Safety, tolerability and pharmacokinetics of fesoterodine in patients with hepatic impairment.* ICS/IUGA Ann Meet. Paris, France, Aug. 25-27 2004.

21. *Concomitant food intake does not signficantly influence the pharmacokinetics of the novel, bladder-selective antimuscarinic fesoterodine.* ICS/IUGA Ann Meet. Paris, France, Aug. 25-27 2004.

22. *Fesoterodine, a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome: Results of a phase 2 controlled study*. ICS/IUGA Ann Meet. Paris, France, Aug. 25-27 2004.

23. Data on file Schwarz BioSciences.

24. Schwarz Pharma Annual Report 2003.